PRECLINICAL STUDIES SUPPORT CLINICAL DEVELOPMENT OF AZD2936, A MONOVALENT BISPECIFIC HUMANIZED ANTIBODY TARGETING PD-1 AND TIGIT

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Background Although checkpoint inhibition has improved the treatment of metastatic non-small cell lung cancer (NSCLC), up to 65% of patients progress after initial response to PD-1/PD-L1 targeting strategies, suggesting additional immune therapies are required to further improve patient outcome. TIGIT is a receptor of the Ig superfamily, which plays a role of limiting T cell and NK cell activity. TIGIT expression has high correlation with PD-1 and both are expressed on dysfunctional tumor-infiltrating lymphocytes. Here we introduce AZD2936, a monovalent, bispecific, humanized IgG1 antibody that specifically binds to human TIGIT and PD-1 with high affinity and enhances T cell activity within preclinical models. AZD2936 is currently being evaluated in a Phase I/II study in participants with advanced or metastatic NSCLC, NCT04995523.

Methods Primary human immune cells and cells engineered to express either PD-1 and TIGIT or their ligands were co-cultured and incubated with AZD2936 to investigate its impact on T cell activation, cytokine production and cytotoxicity. Immune-compromised NSG mice bearing human tumors and administered human T cells were used to investigate the effect of AZD2936 on tumor growth and survival.

Results AZD2936 individually and concurrently bound TIGIT and PD-1 with high affinity and blocked interaction with their primary ligands, CD155 and PD-L1, respectively. The bispecific antibody triggered antigen-specific T cell-mediated lysis of tumor cell lines and enhanced IFN-γ release as compared to anti-PD-1 treatment. Co-culture of antigen specific T cells in a tumor spheroid model showed an increase in tumor cell killing with the addition of AZD2936. The activity of AZD2936 was also investigated in two xenograft mouse models of human cancer. In these models, administration of AZD2936 to animals significantly inhibited tumor growth compared to controls and a combination of parental antibodies.

Conclusions AZD2936 represents a novel immunotherapy engineered to target PD-1 and TIGIT with the potential to enhance anti-tumor immunity. These preclinical results support the ongoing clinical development of AZD2936 in patients with cancer.

Trial Registration NCT04995523

REFERENCES

Ethics Approval All animal studies were carried out in accordance to IACUC protocol 21-15